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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/645,769	10/25/2000	Darwin J Prockop	9598-101U2(99-0356)	4022

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AKIN, GUMP, STRAUSS, HAUER & FELD, L.L.P.  
ONE COMMERCE SQUARE  
2005 MARKET STREET, SUITE 2200  
PHILADELPHIA, PA 19103

EXAMINER

SHUKLA, RAM R

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 06/05/2002

8

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

09/695,769

Applicant(s)

PROCKOP ET AL.

Examiner

Ram Shukla

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☐ Claim(s) 1-41 is/are pending in the application.
- 4a) Of the above claim(s) 30 and 37-41 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☐ Claim(s) 1-29 and 31-36 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

### DETAILED ACTION

1. Applicant's election without traverse of the invention of group I, claims 1-29 and 31-36 in Paper No. 7, is acknowledged.

2. Claims 30 and 37-41 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 7.

### ***Claim Rejections - 35 USC § 112***

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-29 and 31-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "the isolated cells" in line 1. There is insufficient antecedent basis for this limitation in the claim because it is unclear as to whether this term refers to isolated human marrow stromal cells in line 1 or the isolated cells in line 2.

Claim 1 recites the limitation "the cells" in line 6. There is insufficient antecedent basis for this limitation in the claim because it is unclear as to whether it refers to cells recited in lines 1, 3, or 4.

Claims 3-11 recite the limitation "the cells" in line 1. There is insufficient antecedent basis for this limitation in the claim because it is unclear as to which cells this term is supposed to refer to since cells are recited in lines 1, 3, 4, and 6.

Claim 12 recites the limitation "harvested cells" in line 1. There is insufficient antecedent basis for this limitation in the claim because neither this claim nor claim 1 recites this term.

Claim 12 recites the limitation "the cells" in 4. There is insufficient antecedent basis for this limitation in the claim because claim 1 recites different cells several times and claim 12 recites harvested cells and it is unclear as to which cells this term is referring to.

Claim 13 recites the limitation "the cells" in 4. There is insufficient antecedent basis for this limitation in the claim because claim 1 recites different cells several times and claim 12 recites harvested cells and it is unclear as to which cells this term is referring to.

It is noted that the applicants have used several terms "isolated human marrow stromal cells", "the isolated cells", "the cells", and "harvested cells" interchangeable in claims 1-29 and 31-36 which is confusing. Applicants are advised to use these terms consistently and use the terms "said isolated human marrow stromal cells" or "said harvested cells" and also refer them to the step of a method of a claim.

***Claim Rejections - 35 USC § 102***

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

6. Claims 1-21 are rejected under 35 U.S.C. 102(b) as anticipated by Bruder et al (Journal of Cellular Biochemistry 64:278-294, 1997).

Bruder et al teach a method of culturing human mesenchymal stem cells, their characterization, growth kinetics, and osteogenic potential. This art teaches that when bone marrow cells are plated onto tissue culture dish at a density of  $10^7$  cells per  $60 \text{ cm}^2$  adherent human mesenchymal cells represent approximately 1 cell in  $10^5$  nucleated cells. This would mean there are 100 cells in a  $60 \text{ cm}^2$  dish (see the left column on page 280). The growth medium contains fetal bovine serum and the art teaches to go through multiple serial passaging (see figure 1). Accordingly, the art of Bruder et al would meet the limitations of the claimed invention.

7. Claims 1-21 are rejected under 35 U.S.C. 102(b) as being anticipated by Kuznetsov et al (Journal of Bone and Mineral Research 12:1335-1347, 1997).

Kuznetsov et al teach single colony derived strains of human marrow stromal fibroblasts (HMSF) cells. Second paragraph in the left column of page 1337 teaches the method of singly colony derived HMSF which comprising plating cells at  $.14-14 \times 10^3 \text{ cells/cm}^2$  or  $0.007 - 3.5 \times 10^3 \text{ cells/cm}^2$ . The art also teaches multiple passaging and cell culture medium comprised fetal bovine serum (see the last paragraph in the right column on page 1336).

Accordingly, this art anticipates the claimed invention.

8. Claims 1-21 are rejected under 35 U.S.C. 102(a) as being anticipated by DiGirolamo et al (British Journal of Haematology 107:275-281, 1999).

DiGirolamo et al teaches a method of culturing human marrow stromal cells and using a colony forming assay to identify cells that have the greatest potential to propagate and differentiate. The art teaches to culture cells at a density of about 10 cells per  $\text{cm}^2$  in 100 mm tissue culture dishes in a culture medium supplemented with fetal calf serum (see the isolation and culture of hMSCs and CFU-F assays in the left column continued in the right column on page 276). The art also teaches multiple passaging of the cells.

Accordingly, this art anticipates the claimed invention.

***Claim Rejections - 35 USC § 103***

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

10. Claims 1 and 22-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuznetsov et al (Journal of Bone and Mineral Research 12:1335-1347, 1997) in view of Azizi et al (Proc. Natl. Acad. Sci. USA 95:3908-3913, 1998).

Kuznetsov et al teach single colony derived strains of human marrow stromal fibroblasts (HMSF) cells. Second paragraph in the left column of page 1337 teaches the method of singly colony derived HMSF which comprising plating cells at  $.14-14 \times 10^3$  cells/cm<sup>2</sup> or  $0.007 - 3.5 \times 10^3$  cells/cm<sup>2</sup>. The art also teaches multiple passaging and cell culture medium comprised fetal bovine serum (see the last paragraph in the right column on page 1336). This art does not teach to add a growth factor to the culture medium for growing human marrow stromal cells.

Azizi et al teaches growing of human marrow stromal cells and addition of PDGF-AA to the culture (see figure 1 and the first paragraph of the results section on page 3910 continued on page 3911).

At the time of the invention, it would have been obvious to an artisan of ordinary skill to modify the culture conditions of Kuznetsov et al and add PDGF-AA to the culture medium as used by Azizi et al with a reasonable expectation of success. An artisan would have been motivated to add PDGF-AA to the culture medium because PDGF-AA increases the growth rate of marrow stromal cells as taught by Azizi et al.

11. Claims 1, 24-29 and 31-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuznetsov et al and Azizi et al as applied to claims 22-23 above,

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and further in view of Greenberger et al (US Patent No 5,766,950, 6-16-1998) and Prockop (Science 276:71-74, 1997).

Teachings of Kuznetsov et al and Azizi et al have been summarized in paragraph 10 previously. None of these articles teaches supplementing the growth medium for culturing human marrow stromal cells with a growth factor present in conditioned medium.

Greenberger teaches a method for selection and expansion of stromal cells, wherein the cells are grown in a vessel pre-coated with fibroblast growth factor and the cell culture is maintained in the presence of conditioned medium (see lines 1-51 in column 6).

Prockop reviews the state of the art of marrow stromal cells, their isolation, characteristics, and growth properties in cell culture. For example, these cells secrete cytokines and growth factors, such as IL-1, IL-6, CSF-1, CSF (see the right column on page 72).

At the time of the invention, an artisan of skill would have been motivated to add the conditioned medium to the culture medium of human stromal cells with a reasonable expectation of success, since it was routine in the art to add conditioned medium to stromal cell culture. An artisan would have been motivated to add conditioned medium to the culture because the medium contains growth factors and cytokines that are helpful in the growth of marrow stromal cells. It is noted that while Greenberger does not teach the addition of conditioned medium from cells that are at the density of less than 50 cells per  $\text{cm}^2$ , it would be logical to add the condition medium from cells that are similar in density for maintaining the culture conditions. Regarding the limitations of the molecular weight of the factors, it is noted that the cytokines and growth factors secreted by marrow stromal cells would be in the range of molecular weight recited. Regarding the limitation of colony forming unit as the assay to compare the viability and expandability of the cells, it is noted that it was routine at the time of the claimed invention to use colony forming assay or growing single cell colonies and expand them in vitro to develop cell lines and also for studies. Furthermore, it was routine in the art to compare growth of control cells with that of treated cells for assessing the effect of

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growth factors on growth of marrow stromal cells, for example, see Azizi et al (figure 1).

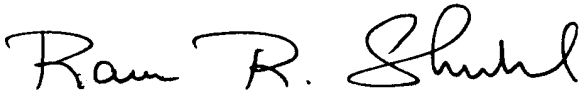
12. No claim is allowed.

When amending claims, applicants are advised to submit a clean version of each amended claim (without underlining and bracketing) according to § 1.121(c). For instructions, Applicants are referred to <http://www.uspto.gov/web/offices/dcom/olia/aipa/index.htm>.

Applicants are also requested to submit a copy of all the pending/under consideration claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Dianiece Jacobs whose telephone number is (703) 305-3388.

Ram R. Shukla, Ph.D.

  
**RAM R. SHUKLA, PH.D**  
**PATENT EXAMINER**